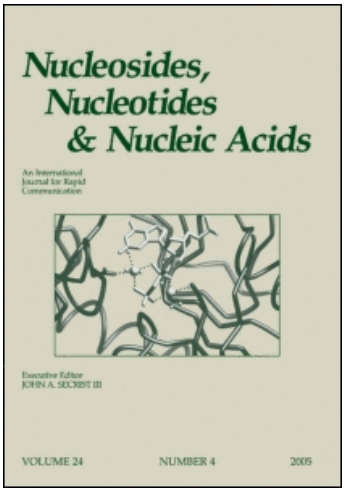

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

SYNTHESIS OF N^6-ALKYLATED ADENOSINE DERIVATIVES

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To cite this Article Lescrinier, E. , Pannecouque, C. , Rozenski, J. , Van Aerschot, A. , Kerremans, L. and Herdewijn, P.(1996) 'SYNTHESIS OF N^6-ALKYLATED ADENOSINE DERIVATIVES', Nucleosides, Nucleotides and Nucleic Acids, 15: 11, 1863 — 1869
To link to this Article: DOI: 10.1080/07328319608002738
URL: http://dx.doi.org/10.1080/07328319608002738

NUCLEOSIDES & NUCLEOTIDES, 15(11&12), 1863-1869 (1996)

SYNTHESIS OF N^6-ALKYLATED ADENOSINE DERIVATIVES

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Abstract. N^6-alkylated adenosine can be synthesized by reduction of the corresponding carboxylic acid amides using $LiAlH_4$. Starting from 2',3'-*O*-isopropylidene adenosine, N^6-ethyladenosine, N^6-propyladenosine, N^6-isobutyladenosine, N^6-benzyladenosine and N^6-furfuryladenosine were obtained in a three step procedure (acylation, reduction, deprotection).

INTRODUCTION

As the adenosine base contains several nucleophilic centers, alkylation of adenosine results in a complex reaction mixture. Therefore alternative pathways have been developed for the synthesis of N^6-alkylated adenosines. Three main pathways described for the synthesis of N^6-alkylated adenosines are a) reaction of N^6-alkylated adenine (obtained from 6-methylmercaptopurine)[1] with a protected ribose moiety under Vorbrüggen conditions[2] b) reaction of an appropriate amine with 6-chloropurine riboside[3-5] and c) a silylation-amination procedure using inosine as starting material[6]. The first approach is rather lengthy and the second approach starts from modified nucleosides wich have to be synthesized first. Approach c is more straightforward and uses inosine as a starting material. As an alternative, we propose the synthesis of N^6-alkylated adenosine by reduction of N^6-acylated 2',3'-*O*-isopropylidene adenosine with $LiAlH_4$ followed by removal of the isopropylidene protection group.

RESULTS AND DISCUSSION

The commercially available 2',3'-*O*-isopropylidene adenosine (1) was acylated according to the transient protection method[7] yielding 2',3'-*O*-isopropylidene-N^6-acetyladenosine **(2a)**, 2',3'-*O*-isopropylidene-N^6-propionyladenosine **(2b)**, 2',3'-*O*-isopropylidene-

N^6-isobutyryladenosine (**2c**), 2',3'-*O*-isopropylidene-N^6-benzoyladenosine (**2d**) and 2',3'-*O*-isopropylidene-N^6-furoyladenosine (**2e**) *(scheme 1)*.

Selective reduction of the N^6-carboxamides **2a-e** was performed in anhydrous 1,4-dioxane using an excess of $LiAlH_4$ *(scheme 2)*. The reaction time at room temperature depends upon the amide side chain *(table 1)*. Longer substituents and branching need longer reaction time. The yield with aromatic amides is low due to the formation of several side products.

Various reaction conditions for the reduction of N^6-benzoyl-2',3'-*O*-isopropylidene adenosine (**2d**) were compared. A suspension of **2d** in tetrahydrofurane was reacted with borane-tetrahydrofurane complex (4moleq/mmol)[8-11], $NaBH_4/I_2$ (2.5 moleq $NaBH_4$, 1 moleq I_2)[12], $LiAlH_4$ (2 moleq and 5 moleq)[13] at different temperature (0°C, room temperature, reflux temperature). Best results were obtained with $LiAlH_4$ in anhydrous dioxane at room temperature. Hydrolysis of the amide bound was observed as side reaction. The isopropylidene protecting group of compounds **3a-e** was removed with 80% aqueous acetic acid solution at 75°C. The obtained N^6-alkylated compounds were easily crystallised from methanol. In conclusion, this approach to *N*-alkylated adenosines is a useful alternative to existing methods, especially for the introduction of aliphatic N^6-subsituents.

GENERAL PROCEDURES

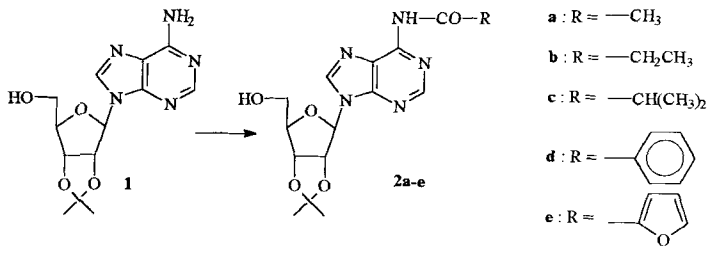
Melting points were determined in capillary tubes on a Büchi-Tottoli apparatus and are uncorrected. The ^1H NMR and ^{13}C NMR spectra were determined on a Varian Gemini 200 spectrometer with tetramethylsilane as internal standard for ^1H NMR and DMSO-d_6 (39.6 ppm) or $CDCl_3$ (76.9 ppm) for the ^{13}C NMR spectra. Mass spectra were recorded on a Concept Kratos 1H mass spectrometer. LSIMS spectra were recorded with thioglycerol as matrix. Main fragments are indicated (intensity in %). Elemental analysis were performed by Laboratory of Anorganic Chemistry, University of Konstanz. Thin layer chromatography (TLC) was performed on Machery-Nagel Alugram Sil G/UV_{254} sheets and spots were examined with UV light and sulfuric acid-anisaldehyde spray. Column chromatography was performed on Janssen Chimica Silicagel (0.060-0.200nm). Anhydrous solvents aceton, pyridine, tetrahydrofurane and dioxane were obtained by refluxing overnight on resp. K_2CO_3, KOH and $LiAlH_4$ followed by distillation.

General reaction for N^6-acylation:

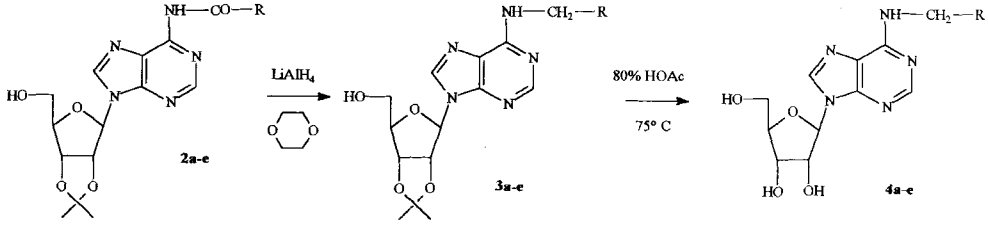
All N^6-acylation reactions were performed as described by Jones *et al.*[7].

General reaction for the amide reduction:

To a solution of compound **2a-e** in anhydrous 1,4-dioxane $LiAlH_4$ (5 moleq) was added under a nitrogen atmosphere at 11°C. The suspension was stirred at room



SCHEME 1



SCHEME 2

TABLE 1: Yield of the reaction steps and time of the reduction reaction.

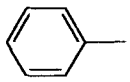
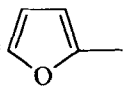
	1 ⟶ 2	2 ⟶ 3	3 ⟶ 4
a: R=CH_3—	45%	61% (1h)	48%
b: R= CH_3CH_2—	52%	78% (4h)	23%
c: R=$(CH_3)_2CH$—	70%	34% (9h)	64%
d: R= 	89%	30% (1h)	42%
e: R= 	53%	32% (20h)	23%

TABLE 2: LSIMS data

	MH^+	BH_2^+	
4a	296 (63)	164 (100)	
4b	310 (63)	192 (100)	
4c	324 (62)	226 (75)	
4d	358 (65)	226 (75)	$C_7H_7^+$ (100)
4e	348 (70)	216 (100)	

TABLE 3: UV data and melting points

	4a	**4b**	**4c**	**4d**	**4e**
melting point (in °C)	193-194	158[3]	157	186[4]	152[14]
UV: λ_{max} (in nm)	267	267	267	269	267
ε	16.600	16.100	17.000	20.900	16.600

TABLE 4: 1H-NMR data

	4a	**4b**	**4c**	**4d**	**4e**
H-2, H-8	8.33-8.20	8.33-8.20	8.33-8.18	8.38-8.20	8.37-8.23
NH	7.85	7.85	7.91	8.46	8.30
H-1'	5.88	5.89	5.88	5.88	5.89
OH-2'	5.46	5.45	5.45	5.46	5.46
OH-5'	5.43	5.45	5.45	5.40	5.37
OH-3'	5.19	5.19	5.19	5.20	5.19
H-2'	4.61	4.61	4.61	4.62	4.59
H-3'	4.14	4.15	4.14	4.14	4.13
H-4'	3.96	3.96	3.96	3.97	3.96
H-5'	3.75-3.48	3.71-3.38	3.70-3.48	3.75-3.48	3.74-3.50
other signals	3.16 ($\underline{CH_2}CH_3$)	3.16 ($\underline{CH_2}CH_2CH_3$)	3.35 ($\underline{CH_2}CH(CH_3)_2$	7.10 (Ar)	7.52 (H5-furan)
	1.17 ($CH_2\underline{CH_3}$)	1.70 ($CH_2\underline{CH_2}CH_3$)	1.99 ($CH_2\underline{CH}(CH_3)_2$	4.72 ($\underline{CH_2}$-Ar)	6.35 (H4-furan)
		0.88 ($CH_2CH_2\underline{CH_3}$)	0.88 ($CH_2CH(\underline{CH_3})_2$		6.22 (H3-furan)
					4.69 ($\underline{CH_2}$-furan)

TABLE 5: 13C-NMR data

	4a	4b	4c	4d	4e
C6	154.7	154.9	155.0	154.6	154.5
C2	152.5	152.5	152.4	152.5	152.9
C4	148.1	148.3	148.2	148.2	148.7
C8	139.8	139.8	139.7	140.1	140.1
C5	117.6	119.6	119.7	120.0	119.8
C1'-C4'	88.1-86.0	88.1-86.0	88.1-86.0	88.0-86.0	88.0-86.0
C2'	73.6	73.6	73.5	73.6	73.6
C3'	70.6	70.8	70.8	70.8	70.7
C5'	61.8	61.8	61.8	61.8	61.7
other signals	34.7 ($\underline{CH_2}CH_3$) 14.9 ($CH_2\underline{CH_3}$)	41.6 ($\underline{CH_2}CH_2CH_3$) 22.4 ($CH_2\underline{CH_2}CH_3$) 11.4 ($CH_2CH_2\underline{CH_3}$)	47.3 ($\underline{CH_2}CH(CH_3)_2$ 27.9 ($CH_2\underline{CH}(CH_3)_2$ 20.2 ($CH_2CH(\underline{CH_3})_2$	128.7; 127.2; 126.7 (Ar) 43.0 ($\underline{CH_2}$-Ar)	152.3 (C2-furan) 141.9 (C5-furan) 110.5 (C4-furan) 106.7 (C3-furan) 48.6 ($\underline{CH_2}$-furan)

TABLE 6: elemental analysis

	formula:	Mr:	elemental analysis					
4a	$C_{12}H_{17}N_5O_4 . H_2O$	313.31	calc.	C 46.00	H 6.11	N 22.35		
			found	46.20	6.07	22.33		
4b	$C_{13}H_{19}N_5O_4.H_2O$	327.34	calc.	C 47.70	H 6.47	N 21.39		
			found	47.34	6.21	21.21		
4c	$C_{14}H_{21}N_5O_4$	323.35	calc.	C 52.00	H 6.55	N 21.66		
			found	52.22	6.59	21.21		
4d	$C_{17}H_{14}N_5O_4$	371.29	calc.	C 57.14	H 5.36	N 19.60		
			found	57.04	5.35	19.45		
4e	$C_{15}H_{17}N_5O_5$. 1 1/3 H_2O	371.29	calc.	C 48.52	H 5.34	N 18.86;		
			found	48.36	5.31	18.74		

temperature and solid $NaHCO_3$ was added and MeOH was dropped into the reaction mixture (11°C) untill no more hydrogen gas was formed. After evaporation the residue was treated with a saturated $NaHCO_3$ solution and extracted three times with ethyl acetate. The combined organic layers were dried on anhydrous $MgSO_4$ and, after filtration, the solvent was evaporated. The residue was purified chromatographically .

Example:

To a solution of compound **2a** (1.22 g, 3.5 mmol) in anhydrous 1,4-dioxane (120 mL) $LiAlH_4$ (0.665 g,17.5 mmol, 5 moleq) was added under a nitrogen atmosphere at 11°C. The suspension was stirred for 1 h at room temperature, solid $NaHCO_3$ and MeOH were added into the reaction mixture (11°C) until no more hydrogen gas was formed. After evaporation the residue was treated with a saturated $NaHCO_3$ solution and extracted three times with ethyl acetate. The combined organic layers were dried on anhydrous $MgSO_4$ and, after filtration, the solvent was evaporated. The residue was purified chromatographically (CH_2Cl_2 : MeOH 95 : 5) affording 0.71 g (2.12 mmol, 61 %) of compound **3a**.

Deprotection:

A 0.05 M solution of compound **3a-e** in 80 % aqueous acetic acid was stirred overnight at 75°C. After evaporation of the solvent, the residue was coevaporated 3 times with ethanol. The residue was purified by crystallisation from MeOH. As all compounds were not completely described in literature, experimental data are given in tables 2-6. Literature references are indicated when available.

Acknowledgment:

This investigation recieved financial support from UNDP/ World BANK/ WHO special program for research and training in tropical deseases.

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Received May 31, 1996
Accepted September 23, 1996